UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,742	07/19/2006	Brett Finlay	27112-14589	2851

758 7590 08/05/2010

FENWICK & WEST LLP
SILICON VALLEY CENTER
801 CALIFORNIA STREET
MOUNTAIN VIEW, CA 94041

EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	**PAPER NUMBER**
1645	

NOTIFICATION DATE	DELIVERY MODE
08/05/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOC@Fenwick.com

Office Action Summary	Application No.	Applicant(s)	
	10/577,742	FINLAY ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-58,71-73 and 86-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-58,71-73 and 86-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A and B*.

DETAILED ACTION

1 The amendment filed 5/17/10 has been entered into the record. Claims 1-52, 59-70 and 74-85 have been cancelled. Claims 53-58, 71-73 and 86-94 are pending and are under examination.

Election/Restrictions

2 Applicant's election without traverse of Group VI claims 53-58 and 71-73 and species NleA in response to the restriction requirement mailed 3/30/09 is acknowledged.

Claims 1-52, 59-70 and 74-85 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/30/09.

Claims 1-52, 59-70 and 74-85 were cancelled and claims 86-94 were added in an amendment filed 12/4/09.

A new restriction requirement further restricting the inventions of claims 53-58, 71-73 and 86-94 was mailed 12/16/09.

Applicant's election with traverse of Group I claims 53-58, 71-73 and 86-94 and the species SEQ ID NO: 24 in response to the restriction requirement mailed 12/16/09 is acknowledged. The traversal is on the ground(s) that the examiner has not, in accordance with Rule 13.2, described how the polypeptide sequences of Group I lack the same or corresponding special technical feature of the nucleic acid molecules of Group II. Instead the examiner appears to have focused on the alleged differences between SEQ ID NO:22 and SEQ ID NO:24 by pointing to the examiner's sequence alignments in Appendices A and B.

This is carefully considered but not found persuasive. According to 37 C.F.R 1.475 (d) and (e) , if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and

the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c) and the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. In the instant cases, multiple uses are being claimed within independent claims 53, 54 and 55 and across independent claims 54-55. The first use being claimed is drawn to a method for eliciting an immune response against an A/E pathogen or component thereof, in an animal comprising administering to the animal an effective amount of a composition substantially identical to the sequence of SEQ ID NOs: 22 and this first use is therefore considered the main invention in the claims. Furthermore, the groups of inventions I and II and the species of the invention (see p. 4 of office action mailed 12/16/09) do not relate to a single general inventive concept under PCT Rule 13.1. Groups I-II and the species lack unity of invention because even though the inventions of these groups require the technical feature of A/E virulence factors, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of Hideo et al (JP20023550742A2, cited in IDS).

Hideo et al (JP20023550742A2, cited in IDS) teaches a composition comprising a polypeptide comprising an amino acid sequence substantially identical (81% identical) to the sequence of SEQ ID NO: 22 or a variant thereof for treating *E. coli* infection. Also see sequence alignment attached previously as Appendix A in the office action mailed 12/16/09. The definition of substantially identical on p. 13 of the instant specification allows for variants of SEQ ID NO: 22. Hideo et al teaches a method of treating an infection with *E. coli* O 157:H7, an A/E pathogen with said polypeptide See English abstract cited in IDS. Thus, Hideo anticipates the main invention in the claims and therefore, Group I lacks unity with Group II and the species also lack unity.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3 Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

4 The drawings in this application have been accepted. No further action by Applicant is required.

Specification

5 The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See p.54-55.

Information Disclosure Statement

6 The information disclosure statement filed 5/19/09 has been considered. An initialed copy is enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7 Claims 53-58, 71-73 and 86-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or
iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby eliciting an immune response in the animal.

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or
iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing colonization of the A/E pathogen in the animal.

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof,
or iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing shedding of the A/E pathogen in the animal.

The specification teaches that the term "antigenic peptide" refers to a peptide that is recognized by an antibody. Usually, the immune response results in the production of antibodies recognizing the antigenic peptide or at least a part thereof. See p. 5.

The specification teaches that "a substantially identical" sequence is an amino acid or nucleotide sequence that differs from a reference sequence only by one or more conservative substitutions, as discussed herein, or by one or more non-conservative substitutions, deletions, or insertions located at positions of the sequence that do not destroy the biological function of the amino acid or nucleic acid molecule. Such a sequence can be any integer from 10% to 99%, or more generally at least 10%, 20%, 30%, 40%, 50, 55% or 60%, or at least 65%, 75%, 80%, 85%, 90%, or 95%, or as much as 96%, 97%, 98%, or 99% identical at the amino acid or nucleotide level to the sequence used for comparison using, for example, the Align Program (96) or FASTA. See p. 13

Thus, the claims are drawn to a large genus of variants of SEQ ID NO: 24 comprising species that are fragments of SEQ ID NO: 24, substitution , deletion and/or insertion variants of SEQ ID NO: 24 and substitution , deletion and/or insertion variants of fragments or variants of SEQ ID NO: 24 The scope of the claims encompasses numerous structural species resulting in a highly variant genus composed of members with a significant number of structural differences. Up to >90% of the sequence of SEQ ID NO: 24 or fragments or variants of SEQ ID NO: 24 can be substituted, deleted and/or inserted. The claim requires that these genus of variants have the property of stimulating an immune response against any A/E pathogen (including treating or preventing) infection in a animal and reducing colonization or shedding of any A/E pathogen.

The specification describes an actual reduction to practice of SEQ ID NO: 24 but does not reduce to practice fragments or variants thereof or proteins comprising an amino acid sequence substantially identical (i.e. up to >90% of the sequence can be

substituted, deleted and/or inserted) to SEQ ID NO: 24 or fragments or variants thereof that induce an immune response against any A/E pathogen (including treating or preventing) infection in a animal and reducing colonization or shedding of any A/E pathogen.

The specification does not describe the common structure of the genus of variants or fragments of SEQ ID NO: 24 and proteins comprising amino acid sequence that is substantially identical (see broad definition of "substantially identical" above) that correlates with the property of stimulating an immune response against any A/E pathogen (including treating or preventing) infection in a animal and reducing colonization or shedding of any A/E pathogen.

There are no sufficient identifying characteristics of fragments of SEQ ID NO: 24 or variants of fragments or variants of variants of SEQ ID NO: 24; these variants are described only by a functional characteristic (stimulating an immune response against any A/E pathogen including treating or preventing infection in animal and reducing colonization or shedding of any A/E pathogen), without any known or disclosed correlation between the biological function and structural characteristics. *In re Bell* F.2d 781, 26 USPQ2d (Fed. Cir 1993).

It is unpredictable from the disclosure of SEQ ID NO: 24 which members of the large and variant genus will stimulate an immune response against any A/E pathogen (including treating or preventing) infection in animal and reducing colonization or shedding of any A/E pathogen. Colman et al (Research in Immunology 145: 33-36, 1994, p.33 column 2, p. 35 column 1) disclose that single amino acid changes in an antigen can effectively abolish the interaction with an antibody entirely and that a very conservative amino acid substitution may abolish antibody binding and a non-conservative amino substitution may have little effect in antibody binding. Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24): "One

could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool."

Even though one could screen for variants of SEQ ID NO: 24 that stimulate an immune response against any A/E pathogen (including treating or preventing) infection in animal and reducing colonization or shedding of any A/E pathogen, the courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus or how to identify their common structural features. The written description requirement is separate and distinct from the enablement requirement (See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004) and adequate written description requires more than a mere reference to a potential method for identifying candidate polypeptides. The purpose of the written description requirement is broader than to merely explain how to 'make and use' [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). In such an unpredictable art, as set forth supra, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See *Noelle v Lederman*. 355 F. 3d 1343, 1350, 69 USPQ2d 1508, 1514 (*Fed. Cir. 2004*) and *In re Alonso* (Fed. Cir. 2008-1079).

Therefore, Applicants as of the time of filing were not in possession of the full genus of variants of SEQ ID NO: 24 (see genus set forth above) to which the claims are drawn.

For Further guidance regarding compliance with the written description requirement, Applicants are directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement,

Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, Revision 1 March, 2008 http://www.USPTO.gov/web/menu/written.pdf.

8 Claims 53-58, 71-73 and 86-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for eliciting an immune response against an enterohemorrhagic *E. coli* (EHEC) or SEQ ID NO: 24 (a component of enterohemorrhagic E. coli 0157:H7) or reducing colonization or shedding of enterohemorrhagic *E. coli* (EHEC) or treating enterohemorrhagic *E. coli* (EHEC) infection, in an animal comprising administering to the animal an effective amount of a composition or cell culture supernatant comprising:
i) a polypeptide which comprises the amino acid sequence set forth in SEQ ID NO: 24, does not reasonably provide enablement for:

preventing infection by enterohemorrhagic E. coli (EHEC) in an animal comprising administering to the animal an effective amount of a composition or cell culture supernatant comprising: i) a polypeptide which comprises the amino acid sequence set forth in SEQ ID NO: 24; and

a method for eliciting an immune response against any other A/E pathogen, or component thereof, or reducing colonization or shedding of an A/E pathogen or treating or preventing infection by an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition or cell culture supernatant comprising another polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NO: 24 or a fragment or variant thereof**.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This is a scope of enablement rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, the amount of direction provided by the inventor, the existence of working examples, state of the prior art, the level of predictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention and Breadth of the Claims

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby eliciting an immune response in the animal.

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing colonization of the A/E pathogen in the animal.

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical

to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof,
or iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing shedding of the A/E pathogen in the animal.

Claim 90 is drawn to treating or preventing an infection by the A/E pathogen.

The specification on p. 13 teaches that "a substantially identical" sequence:

is an amino acid or nucleotide sequence that differs from a reference sequence only by one or more conservative substitutions, as discussed herein, or by one or more non-conservative substitutions, deletions, or insertions located at positions of the sequence that do not destroy the biological function of the amino acid or nucleic acid molecule. Such a sequence can be any integer from 10% to 99%, or more generally at least 10%, 20%, 30%, 40%, 50, 55% or 60%, or at least 65%, 75%, 80%, 85%, 90%, or 95%, or as much as 96%, 97%, 98%, or 99% identical at the amino acid or nucleotide level to the sequence used for comparison using, for example, the Align Program (96) or FASTA.

Furthermore, p. 18 of the specification defines an "immune response" as follows:

An "immune response" includes, but is not limited to, one or more of the following responses in a mammal: induction of antibodies, B cells, T cells (including helper T cells, suppressor T cells, cytotoxic T cells, y5 T cells) directed specifically to the antigen(s) in a composition or vaccine, following administration of the composition or vaccine. An immune response to a composition or vaccine thus generally includes the development in the host mammal of a cellular and/or antibody- mediated response to the composition or vaccine of interest. In general, the immune response will result in prevention or reduction of infection by an A/E pathogen; resistance of the intestine to colonization by the A/E pathogen; or reduction in shedding of the A/E pathogen.

The breadth of A/E (attaching and effacing) pathogens is broad and includes EHEC, EPEC, EPEC-like animal pathogens that cause disease in rabbits, pigs and mice. See specification lines p. 2 lines 17-20. The specification teaches that in general, the immune response will result in prevention or reduction of infection by an A/E pathogen; resistance of the intestine to colonization by the A/E pathogen; or reduction in shedding of the A/E pathogen. Thus, the breadth of the claims covers the use of SEQ ID NO: 24

or variants that are fragments of SEQ ID NO: 24, substitution, deletion and/or insertion variants of SEQ ID NO: 24 and substitution, deletion and/or insertion variants of fragments or variants of SEQ ID NO: 24 for prevention or reduction of infection by an A/E pathogen; resistance of the intestine to colonization by the A/E pathogen; or reduction in shedding of the A/E pathogen.

Guidance in the specification and the existence of working examples

The specification teaches that SEQ ID NO: 24 aka NleA is derived from enterohemorrhagic *E. coli* (EHEC). See sequence listing annotation for SEQ ID NO: 24.

The specification does not correlate immunogenicity of SEQ ID NO: 24 or variants of SEQ ID NO: 24 (see breadth of variants of SEQ ID NO: 24 set forth above) with preventing infection by any A/E pathogen.

The specification does not correlate immunogenicity of variants of SEQ ID NO: 24 (see breadth of variants of SEQ ID NO: 24 set forth above) with inducing an immune response against any A/E pathogen or reducing colonization or shedding of any A/E pathogen or treating A/E pathogen infection.

Furthermore, the specification does not correlate immunogenicity of SEQ ID NO: 24 or variants of SEQ ID NO: 24 with cross protection against another A/E pathogen i.e. is not EHEC such as EPEC, EPEC-like animal pathogens that cause disease in rabbits, pigs and mice

State of the prior art and the level of predictability in the art

The art teaches that there are no vaccines available for A/E pathogens such as EHEC or EPEC (Horne et al. Expert Rev. Vaccines 1 (4), 483-493 (2002)., see p. 486 column 2 under vaccine development) and that several vaccine candidates are being investigated (see p. 487-490 under current status of vaccine development).

Vaccines induce protection against infections by stimulating the development of long-lived effector cells and memory cells (Abbas et al. Cellular and Molecular Immunology 2000 Chapter 15 p. 360-362). Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is

insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [PIotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen".

As to the use of variants of SEQ ID NO: 24 to induce an immune response against any A/E pathogen or reducing colonization or shedding of any A/E pathogen or treating or preventing an A/E pathogen infection, Colman et al (Research in Immunology 145: 33-36, 1994, p.33 column 2, p. 35 column 1) disclose that single amino acid changes in an antigen can effectively abolish the interaction with an antibody entirely and that a very conservative amino acid substitution may abolish antibody binding and a non-conservative amino substitution may have little effect in antibody binding. Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool."

In the instant case, the specification does not provide a correlation of the immune response generated by variants of SEQ ID NO: 24 with induction of an immune response against any A/E pathogen or reducing colonization or shedding of any A/E pathogen or treating or preventing an A/E pathogen infection. There is no correlation

between protective T cell response or antibody response by variants of SEQ ID NO: 24 with treatment or prevention of A/E pathogen infection.

As to the use of SEQ ID NO: 24 derived from EHEC 0157:H7 for inducing an immune against other A/E pathogens such as, EPEC and EPEC-like animal pathogens that cause disease in rabbits, pigs and mice and treating (reducing colonization and shedding) and preventing infection response against , EPEC and EPEC-like animal pathogens that cause disease in rabbits, pigs and mice, it is unpredictable that the EHEC antigen can protect against all these other A/E pathogens of EPEC and EPEC-like animal pathogens. For example, Horne et al teach that different approaches may need to be taken for EPEC compared with EHEC, despite their many conserved virulence factors. Moreover Horne et al teach that while virulence factors are potential targets for vaccine development, they still have to be validated and that the vaccine development is complex (certain vaccination protocols are relatively more successfully at yielding long-lived humoral immune responses than others) and vaccines against A/E pathogens are still in the very early stages of exploratory research and vaccines combining several antigens may be the ultimate choice. See p. 488 columns 1 and 2. Therefore, it is unpredictable that variants of SEQ ID NO: 24 or variants or fragments thereof can be used as a universal antigen for inducing an immune response against all A/E pathogens or for treating and prevention infection by all A/E pathogens.

As to preventing infection, the broadest reasonable interpretation of the term infection merely requires that one microorganism gain entry into the cells of a host. During examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004) (The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation >in light of the specification<.). See MPEP 2111.01. Prophylactic/preventative treatments e.g. vaccines for many infections do not prevent infection i.e. the entry of at least one microorganism but

instead kill the organism once it infects tissues or cells thereby eliminating the infection or reducing microorganism burden, thus reducing or eliminating any disease caused by the infection . Such treatments do not prevent the organism from infecting in the first place. Prevention of infection by a bacterium in general is a very high bar because the vaccine must prevent at least one bacterium from infecting a cell. The instant specification does not provide any evidence for prevention of an infection by an A/E pathogen by administering the instant composition i.e. prevention of at least one single A/E pathogen from infecting an animal.

Amount of Direction Provided by the Inventor

The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.,* 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed

invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. See MPEP 2164.03.

Based on the complexity stated in the art for developing vaccines against A/E pathogens, one of skill in the art cannot reasonably extrapolate the immunogenicity of SEQ ID NO: 24 to predict of efficacy for inducing an immune response to all A/ E pathogens or treating (including reducing colonization or shedding) and preventing A/E pathogen infection. One of ordinary skill in the art also cannot reasonably predict the efficacy of variants of SEQ ID NO: 24 (see breadth of these variants set forth above) for inducing an immune response to all A/ E pathogens or treating (including reducing colonization or shedding) and preventing A/E pathogen infection as a protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is not able to induce an immune response to all A/ E pathogens or treat (including reducing colonization or shedding) and preventing A/E pathogen infection. Thus, undue experimentation would be required of the skilled artisan to practice the full scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9 Claims 53-58, 71-72 and 86-94 are rejected under 35 U.S.C. 102(b) as being rejected by Finlay et al. WO 02/053181 (cited in IDS) as evidenced by Hideo et al. (JP20023550742A2, cited in IDS, see partial translation attached as Appendix B).

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby eliciting an immune response in the animal.

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing colonization of the A/E pathogen in the animal.

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof,

or iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing shedding of the A/E pathogen in the animal.

Finlay et al teach a method for eliciting an immune response against an A/E pathogen or component thereof or a method for reducing colonization of an A/E pathogen or a method of reducing shedding (thus treating an infection by an A/E pathogen) in an animal comprising administering to the animal an effective amount of a composition comprising a culture supernatant comprising a polypeptide which comprises an amino acid sequence substantially identical to SEQ ID NO: 24. See p. 37-39 claims 1-26. Said culture supernatant is prepared from *E. coli* EHEC O157:H7 under identical conditions as the instant specification (see example 1 and compare to preparation of cell culture supernatant to maximize the synthesis of cell culture supernatant proteins on p. 23 of Finlay et al) under which a protein comprising the sequence of SEQ ID NO: 24 or NleA (see annotation for SEQ ID NO: 24 in sequence listing) is produced. As evidenced by Hideo et al E. coli EHEC O157:H7 (see Appendix A disclosing a protein 100% identical to SEQ ID NO: 24) makes a protein comprising the sequence of SEQ ID NO: 24. Since Finlay et al teach a culture supernatant prepared from E. coli EHEC O157:H7 under identical conditions as in the instant composition, said culture supernatant is a composition or culture supernatant which comprises a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 and inherently comprises 20% of the cell protein present in the composition. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Also, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668

(Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency). See MPEP2112 (I and II).

Said animal is a human or bovine or ovine. See p. 12 3rd full paragraph.

Said A/E pathogen is enterohemorrhagic E. coli 0157:H7 or E. coli 0157:NM. See p. 37 claims 2-3.

Said composition comprises pharmaceutically acceptable carrier (p. 18 last paragraph) and further comprises EspA, EspB, EspD, EspC, intimin and Tir (see p. 23 example 1 and figure 1 and p. 37claim 9). Said composition further comprises an adjuvant (see p. 19 and p. 37 claims 4-8).

10 Claims 53-58, 71-72, 86, and 88-94 are rejected under 35 U.S.C. 102(b) as being rejected by Wright. US 5,730,989 (3/24/98) as evidenced by Hideo et al (JP20023550742A2, cited in IDS).

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition

comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof.

Wright disclose a method for eliciting an immune response against E. coli 0157:H7 or component thereof, in an animal comprising administering to the animal an effective amount of inactivated E. coli 0157:H7. Said E. coli 0157:H7 is a composition that comprises a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 as evidenced by Hideo et al (see Appendix A disclosing a protein 100% identical to SEQ ID NO: 24). See columns 1-2, column 3 lines 40-67 and column 4. Wright et al disclose a method for treating E. coli infection, thus treatment of the E. coli infection will result in reduction in colonization of E. coli in an animal and result in reduction in shedding of E. coli in an animal.

Said animal is a ruminant i.e. bovine or cattle or human (see column 1 lines 45-65). Said composition comprises a pharmaceutically acceptable carrier and/or adjuvant (column 1 lines 10-17, column 2 lines 50-63, columns 9-11, claims 1-8, 11-21 and 24-26). Since said composition is the whole cell bacteria said composition further comprises EspA, EspB, EspD, EspC, EspP, Shiga toxin 1 and 2, intimin and Tir.

11 Claims 53-55, 71-72, 86 and 90 are rejected under 35 U.S.C. 102(b) as being rejected by Hideo et al (JP20023550742A2, cited in IDS) as evidenced by Wright et al US 5,730,989 (3/24/98).

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof.

Hideo et al discloses a method of eliciting an immune response against E. coli O157:H7 comprising administering a effective amount of composition for inducing an immune response against E. coli O157:H7 comprising a protein 100% identical to SEQ ID NO: 24 (see Appendix A for sequence alignment of SEQ ID NO: 24 with the protein of Hideo et al which includes abstract for the sequence annotation). See abstract, claim 4 and claim 14). Hideo et al also discloses treating an infection by E. coli O157:H7 using said composition (see abstract). Thus treatment of the E. coli infection will result in reduction in colonization of E. coli in an animal and result in reduction in shedding of E. coli in an animal. It is inherent that methods of Hideo et al are to be practiced in animals. As evidenced by Wright et al US 5,730,989 (3/24/98), E. coli O157:H7 infects animals (see column 1). Said composition comprises a pharmaceutically acceptable carrier (see claim 14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12 Claims 53-58, 71-72, 86 and 90-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hideo et al (JP20023550742A2, cited in IDS) in view of Wright et al US 5,730,989 (3/24/98).

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal

an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof.

Hideo et al discloses a method of eliciting an immune response against E. coli O157:H7 comprising administering a effective amount of composition for inducing an immune response against E. coli O157:H7 comprising a protein 100% identical to SEQ ID NO: 24 (see Appendix A for sequence alignment of SEQ ID NO: 24 with the protein of Hideo et al which includes abstract for the sequence annotation). See abstract, claim 4 and claim 14). Hideo et al also discloses treating an infection by E. coli O157:H7 using said composition (see abstract). Thus treatment of the E. coli infection will result in reduction in colonization of E. coli in an animal and result in reduction in shedding of E. coli in an animal. It is inherent that methods of Hideo et al are to be practiced in animals. As evidenced by Wright et al US 5,730,989 (3/24/98), E. coli O157:H7 infects animals (see column 1). Said composition comprises a pharmaceutically acceptable carrier (see claim 14).

Hideo et al does not disclose that the animal is a ruminant or bovine or ovine or human.

Wright et al teaches that E. coli or E. coli O157:H7 infects cattle, lamb and humans and causes diarrhea. See column 1.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to have used the method of Hideo et al for animals such as cattle, lamb and humans, thus resulting in the instant invention with a reasonable expectation of success. The motivation to do so is because Wright et al teach that E. coli or E. coli O157:H7 infects cattle, lamb and humans and causes diarrhea and also to treat infection of cattle and lamb and thus prevent outbreaks associated with consuming dairy products from cattle and lamb.

13 Claims 53-55, 71-72, 86, 88-89 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hideo et al (JP20023550742A2, cited in IDS) as evidenced by Wright et al in view of Finlay et al. WO 02/053181, cited in IDS..

Claim 53 is drawn to a method for eliciting an immune response against an A/E pathogen, or component thereof, in an animal comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or
iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby eliciting an immune response in the animal.

Claim 54 is drawn to a method for reducing colonization of an A/E pathogen in an animal, the method comprising administering to the animal an effective amount of a composition comprising:
i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof, or
iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid

sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing colonization of the A/E pathogen in the animal.

Claim 55 is drawn to a method for reducing shedding of an A/E pathogen in an animal comprising administering to the animal an effective amount of a composition comprising:

i) a polypeptide which comprises an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24 or a fragment or variant thereof,

or iv) a cell culture supernatant which comprises a polypeptide comprising an amino acid sequence substantially identical to the sequence of SEQ ID NOs: 24, or a fragment or variant thereof, thereby reducing shedding of the A/E pathogen in the animal.

Hideo et al discloses a method of eliciting an immune response against E. coli O157:H7 comprising administering a effective amount of composition for inducing an immune response against E. coli O157:H7 comprising a protein 100% identical to SEQ ID NO: 24 (see Appendix A for sequence alignment of SEQ ID NO: 24 with the protein of Hideo et al which includes abstract for the sequence annotation). See abstract, claim 4 and claim 14). Hideo et al also discloses treating an infection by E. coli O157:H7 using said composition (see abstract). Thus treatment of the E. coli infection will result in reduction in colonization of E. coli in an animal and result in reduction in shedding of E. coli in an animal. It is inherent that methods of Hideo et al are to be practiced in animals. As evidenced by Wright et al US 5,730,989 (3/24/98), E. coli O157:H7 infects animals (see column 1). Said composition comprises a pharmaceutically acceptable carrier (see claim 14).

Hideo et al does not disclose that the composition further comprises EspA, EspB, EspD, EspC, intimin and Tir or further comprises an adjuvant.

Finlay et al teach a method for eliciting an immune response against E. coli EHEC O157:H7 or component thereof or a method for reducing colonization of an A/E pathogen or a method of reducing shedding (thus treating an infection by an A/E pathogen) in an animal comprising administering to the animal an effective amount of a

composition comprising a culture supernatant (see p. 37-39 claims 1-26) wherein the composition comprises EspA, EspB, EspD, EspC, intimin and Tir (see p. 23 example 1 and figure 1 and p. 37claim 9) and/or further comprises an adjuvant (see p. 19 and p. 37 claims 4-8).Finlay et al teaches that said composition treats the EHEC infection and/or reduces colonization of the animal. See p. 2 under summary of the invention. Finlay et al teach that administration of said composition to an animal stimulates an immune response against one or more secreted antigens, such as EspA and Tir, which blocks attachment of the EHEC to intestinal epithelial cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to have combined the composition of Hideo et al with that of Finlay et al, thus resulting in the instant method (wherein the composition further comprises EspA, EspB, EspD, EspC, intimin and Tir or further comprises an adjuvant) with a reasonable expectation of success. The motivation to do so is because both compositions are individually taught in the prior art to be useful for the same purpose i.e. inducing an immune response against E. coli EHEC O157:H7 ("It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)) and Finlay et al provides additional motivation in that administration of said composition to a animal stimulates an immune response against one or more secreted antigens, such as EspA and Tir, that blocks attachment of the EHEC to intestinal epithelial cells.

Status of the Claims

Claims 53-58, 71-72 and 86-94 are rejected. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is (571)272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645